McNeil Healthcare (Ireland) Ltd.

a Johnson & Johnson company

21st May 2014

Domperidone: new recommendations to minimise the cardiac risks

Dear healthcare professional,

This letter is to inform you of the recent recommendations to minimise the cardiac risks of domperidone after the recent European review on the benefits and risks of the product. This letter is being sent in agreement with the European Medicines Agency and the Irish Medicines Board.

Summary

- The benefit/risk balance of domperidone remains positive in the relief of the symptoms of nausea and vomiting in adults, adolescents and children.

- This review confirms a small increased risk of serious cardiac adverse drug reactions related to the use of domperidone. A higher risk was observed in patients older than 60 years, those taking daily doses of more than 30 mg and those taking QT-prolonging drugs or CYP3A4 inhibitors concomitantly.

- Domperidone should be used at the lowest effective dose for the shortest possible duration. The maximum treatment duration should not usually exceed one week.

- The new recommended doses are:
    - o For adults and adolescents ≥ 35 kg:
      10 mg up to three times daily with a maximum dose of 30 mg per day.
    - o For children and adolescents < 35 kg:
      0.25 mg/kg body weight per intake up to three times daily with a maximum dose of 0.75 mg/kg body weight per day.

- Domperidone products are now contraindicated in patients with severe hepatic impairment, conditions where the cardiac conduction intervals are impaired or could be affected and underlying cardiac diseases such as congestive heart failure, when co-administered with QT-prolonging drugs or potent CYP3A4 inhibitors.

Further information

Domperidone containing products have been authorised nationally in several EU member states since the 1970s and have been available in Ireland under the trade name Motilium® and as generic domperidone.

The cardiac risks of medicinal products containing domperidone have been under monitoring for several years at national and EU levels. The product information of domperidone containing products has been updated in recent years to reflect the associated risk of QTc prolongation and serious ventricular arrhythmia.

Since then, new cases of serious cardiac adverse reactions related to domperidone use have continued to be reported, leading the Belgian medicines agency to trigger a European re-evaluation of the cardiac risks in the context of the benefits in order to determine whether the marketing authorisations for domperidone-containing products should be maintained, varied, suspended or withdrawn across the EU.

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This review confirmed the risk of serious cardiac adverse drug reactions related to domperidone use including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death. Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, those taking daily doses of more than 30 mg, and in those taking other QT-prolonging drugs or CYP3A4 inhibitors concomitantly.

Based on available data, it is considered that the efficacy of domperidone is established in the relief of nausea and vomiting symptoms, and not established in other indications.

Overall, the benefit/risk balance of domperidone remains positive only for oral formulations (oral solid formulations dosed at 10 or 5 mg and oral solution) and adult suppositories (30 mg).

Finally, it was concluded that risk minimisation measures are necessary in order to improve the benefit/risk balance including restricted indications, use of lower doses, shorter treatment duration, addition of contraindications, warning and precautions. In addition, in order to accurately measure and administer the doses to paediatric patients, oral suspensions should be given using an adapted graduated oral syringe.

The Product Information of all domperidone containing products will be updated to reflect these recommendations.

Call for reporting

Please remember that any suspected adverse reaction should be reported to the Irish Medicines Board using the online system at www.imb.ie or alternatively using the freepost Yellow Card reporting system. Adverse reactions can also be reported to the IMB by calling (01) 6764971.

Suspected adverse reactions may also be reported directly to McNeil Healthcare (Ireland) Ltd. by telephone on 1850 22 00 44.

If you require further information, please contact:

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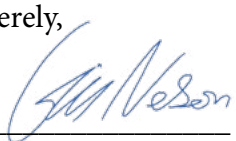
Sincerely,



Dr. Gill Nelson
Medical Director